Model organisms in Inherited Metabolic Disease Research Symposium

September 5, 2025 | Kyoto, Japan

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Location: **Room E** (Kyoto International Conference Centre)

Time: 13:30-15:00 (Sept 5, 2025)

Symposium chairs: Dr Travis Johnson, La Trobe University
Assoc. Prof Matthew Piper, Monash University

13:30-13:35	Welcome to MO-IMD!
13:35 – 13:50	*Caenorhabditis elegans as an invertebrate model for human 3-Hydroxy-3-Methylglutaryl-Coenzyme A Lyase Deficiency.* **Jörn Oliver Sass**, Bonn-Rhein-Sieg University of Applied Sciences, Germany
13:50 – 14:05	*Treatment screening for inherited amino acid disorders: Insights from Drosophila.* **Sarah Mele**, La Trobe University, Australia
14:05 – 14:20	*Drosophila as an in vivo platform to interpret human variants.* **Atsushi Sugie**, Kyoto Institute of Technology, Japan
14:20 – 14:35	*A fluorescent reporter for measuring lipophagy in zebrafish and its application for potential diagnosis of lysosomal storage disorders*. **Siyang Ding**, La Trobe University, Australia
14:35-14:50	*Neuroscience and human disease studies in zebrafish.* **Koichi Kawakami**, Choju Medical Institute, Aichi, Japan
14:50-15:00	Closing remarks

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Abstracts:

Jörn Oliver Sass, Bonn-Rhein-Sieg University of Applied Sciences, Germany

Caenorhabditis elegans as an invertebrate model for human 3-Hydroxy-3-Methylglutaryl-Coenzyme A Lyase Deficiency

Human 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency, due to variants in the HMGCL gene, is a rare autosomal recessive disease with impaired ketogenesis and leucine catabolism. Most patients present within the first year of life with a metabolic decompensation, which can lead to neurological damage or death. As a basis for further pathobiochemical studies we have now investigated a Caenorhabditis elegans (C. elegans) strain, which possesses a mutation in the ortholog of the human HMGCL gene. After confirming that the mutation indeed affects the enzyme activity, it was investigated whether the mutation showed neurological involvement and what impact it had on the life expectancy and physiological development of the worms. A reduced touch response, a delay in its development and a decreased egg-laying rate, as well as a reduced enzyme activity was observed , while osmotic avoidance, egg viability and life span were unaffected. The results are compatible with impairment of the nematode‘s energy supply and possible accumulation of toxic metabolites. This makes C. elegans a suitable model organism for 3-methyl-3-hydroxyglutaryl coenzyme A lyase deficiency and suggests its use in further research on inborn errors of amino acid metabolism.

Sarah Mele, La Trobe Institute for Molecular Science, La Trobe University, Australia

Treatment screening for inherited amino acid disorders: Insights from *Drosophila*

Amino acid disorders (AADs) are a large and heterogenous group of conditions that account for nearly one-third of all cases of inherited metabolic disease. AADs often cause severe neurological and physical decline that can be ameliorated by diet modification. Despite this therapeutic potential, fewer than 40% of AADs have treatments that show any clinical benefit, with many remaining untested. Drosophila has emerged as a tractable tool for AAD treatment screens due to its high genetic and metabolic conservation with humans, ease of scalability, and availability of a synthetic customizable diet. Here we report findings from a Drosophila model of 3-hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency, a disorder of valine catabolism. We show that carnitine supplementation and branched-chain amino acid restriction ameliorate discrete phenotypes of the disease. Conversely, a screen of 100 amino acid combinations revealed a dose-dependent response to tyrosine restriction. These interactions provide insights for further exploration in higher-order model organisms, filling the gaps in AAD treatment approaches.

Atsushi Sugie, Kyoto Institute of Technology, Japan

Drosophila as an in vivo platform to interpret human variants

The rapid development of genomic medicine has increased the diagnosis of rare inherited diseases, but has also led to a growing number of Variants of Uncertain Significance (VUS). To determine the pathogenicity of these variants, practical in vivo systems are needed to connect genetic findings with underlying mechanisms. Drosophila provides a simple and efficient model in which patient-derived variants can be tested directly. With available tools, endogenous fly genes can be suppressed by RNAi, and the corresponding human genes or their variants can be expressed to examine functional conservation and disease relevance. We have used this approach in the study of neurological disorders such as Autosomal Dominant Optic Atrophy, showing that fly models reproduce disease-related phenotypes. While our current work has focused on the nervous system, the same framework can be applied to genes involved in metabolic diseases, making Drosophila a useful platform for variant interpretation across different conditions.

Siyang Ding, La Trobe University, Australia

A fluorescent reporter for measuring lipophagy in zebrafish and its application for potential diagnosis of lysosomal storage disorders

Lysosomal degradation of lipid droplets (LDs), or lipophagy, occurs through two main routes: the canonical macroautophagy machinery and direct lysosome-LD interactions. Both pathways ultimately rely on lysosomes for the degradation of lipid cargo. Lipophagy plays a vital role in mobilizing free fatty acids to meet energy demands during nutrient deprivation and in maintaining lipid homeostasis. However, unlike protein- or organelle-selective autophagy, which can be monitored using genetically encoded fluorescent markers, lipophagy poses a unique challenge due to the lipid-dense nature of LDs. Although various small-molecule dyes exist for general LD imaging, there remains a critical gap in tools capable of specifically reporting on lipophagy activity.To this end, we designed and synthesized a new small-molecule fluorophore, LD-AUTag1. LD-AUTag1 functions as a dual-channel reporter: green fluorescence marks neutral LDs, whereas red fluorescence identifies LD-laden lysosomes, serving as a readout for lipolysosome formation. Quantitative flow cytometric analysis confirmed the probe's utility in distinguishing between treatments that upregulate or suppress lipophagy. Notably, LD-AUTag1 revealed hallmark features of lysosomal dysfunction, such as the accumulation of lipolysosomes and lysosomal swelling, through increased red signal intensity and volume. We further demonstrated the versatility of LD-AUTag1 by applying it to visualize and quantify dynamic lipophagy processes in model organisms including Dictyostelium discoideum and zebrafish. In zebrafish, we found intestine showing the most profound response to drugs that alter lipophagy. Crucially, LD-AUTag1 enabled live primary blood cell-based visualization and early detection of lysosomal storage disorders (LSDs), inborn metabolic errors caused by defective lysosomes, including Niemann-Pick disease type C1 (NP-C1), Batten disease (CLN3), and mucolipidosis IV. The probe demonstrated high sensitivity, effectively distinguishing NP-C1 cells from both wild-type and heterozygous carriers. When applied to immortalized lymphocytes derived from LSD patients, including four Batten disease (CLN3) cases and one mucolipidosis IV case, LD-AUTag1 produced robust, disease-specific signals that were absent in cells from healthy donors. Together, these findings establish LD-AUTag1 as a powerful chemical reporter for quantifying lipophagy and detecting lysosomal damage across multiple organisms and disease models. We anticipate that LD-AUTag1 will offer significant potential as a diagnostic tool for LSDs and as a general probe for studying lipid turnover in health and disease.

Koichi Kawakami, Choju Medical Institute, Aichi, Japan

Neuroscience and human disease studies in zebrafish

Over the past two decades, we have developed a transposon-based gene transfer system applicable to vertebrate cells and established an efficient method for generating transgenic zebrafish. We have also introduced genetic tools such as gene trap, enhancer trap, and the Gal4-UAS system, which allow visualization and manipulation of specific cell types in living animals. In this presentation, I will highlight studies that elucidate functional neural circuits underlying larval and adult zebrafish behaviors using these transgenic approaches. In addition, I will present research employing zebrafish to investigate the causative gene of a rare human neurological disorder.

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